About Physiomics plc

• **Business**
  - Founded 2001, Oxford (UK) based, listed on the LSE (AIM) 2004
  - We use computer modelling to understand and predict optimal cancer therapy.
  - We accelerate the discovery process and reduce development risk.

• **Focus**
  - Cancer
  - Models to simulate drug mechanism of action.
  - Combination therapy and cell populations (SystemCell® Technology).

• **Collaborations:**
  - Eli Lilly
  - Cyclacel Pharmaceuticals
  - ValiRx - Cronos Therapeutics
  - Bayer Technology Services
  - TEMPO (FP6 - EU LifeSciHealth project)
  - Institute of Life Science, Swansea University (HPC)
Chronotherapy for cancer drugs

- Chronotherapy consists of coordinating the timing of a medical treatment with patient’s biological rhythms in order to optimise a drug’s beneficial effects and reduce the undesired ones.
- Tolerability varies in mice and rats by as much as 10-fold for >35 anticancer drugs (e.g. Oxaliplatin, 5-FU, Docetaxel,..) [1]; 2000 patients in Phase I, II & III trials.
- Oxaliplatin was “rescued” using adjusted chronotherapeutic regimes [1].
- Phase III: Oxaliplatin-5FU combination chronotherapy with gender effect (2-Year survival male increase by 25%, but female decrease by 38%) [2].
- Much evidence for circadian regulation of the cell cycle in a variety of cell types [3] and this synchronisation may be lost in tumours [4].

Circadian rhythms

- Highest testosterone secretion: 10:00
- Bowel movement likely: 08:30
- Melatonin secretion stops: 07:30
- Sharpest rise in blood pressure: 06:45
- Lowest body temperature: 04:30
- Deepest sleep: 02:00
- Noon: 12:00
- Best coordination: 14:30
- Fastest reaction time: 15:30
- Greatest cardiovascular efficiency and muscle strength: 17:00
- 18:00: Highest blood pressure
- 19:00: Highest body temperature
- 21:00: Melatonin secretion starts
- 22:30: Bowel movements suppressed

Altered molecular clock in experimental tumors

- Dividing cells: targets for cancer therapeutics
- (no specificity for cancer cells)
- Cell cycle
  - deregulated in cancer cells
  - controlled by circadian timing system in normal cells

Iurisci I. et al., Cancer Res (2006); 10720-8.
TEMPO project

This research is supported by European Commission FP6 Specific Targeted Project TEMPO LSHG-CT-2006-037543

SIXTH FRAMEWORK PROGRAMME

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Tempo (EU project, 8 partners)
General Objectives

- Design 3 to 5 chronotherapeutic schedules based on patient profiling, identified by:
  - Set of 20 to 30 marker genes
  - Cell cycle, drug activity & pattern tolerability & efficacy
  - Addressing gene expression, proteins, signaling pathways, biochemistry
  - Mathematical models

- Application: patient-tailored cancer chronotherapeutics:
  - Seliciclib
  - Irinotecan

- Validation during the project:
  - Optimal schedules in cell cultures, animal models and development of micro-pumps for drug delivery
  - Human prerequisites and theoretical schedules
Therapeutic implications of the interactions between the circadian timing system, the cell division cycle and the pharmacology determinants.
Snapshot of the Mammalian Cell Cycle Model

The diagram shows cell cycle phases & components within a fragment of the mitosis module.

Two wild-type mammalian cell cycles starting from G0 arrest: DNA replication (top) and time courses of cyclins E, D, A & B in complex with cdks (bottom) are shown.
Circadian Clock Model (molecular clock)

Leloup et Goldbeter, PNAS 2003

“16 equations model”
Coupled Cell Cycle - Circadian Clock model

Left: the circadian clock model (dotted orange rectangle) was coupled to the cell cycle model through the CyclinB-cdk1 mitotic switch (red dotted square) via its regulator Wee1. Top: Simulation showing the entrainment of some cell cycle species by the circadian clock.
Virtual FACS - SystemCell® Technology

SAMPLED CELL CYCLE

2N / G1

S-phase

4N / G2

M-phase

4N

S-phase

8N

DRUG ADDITION

2N / G1

S-phase

4N / G2

M-phase

8N

TUNEL

END OF EXPERIMENT
HPC - SystemCell® Technology

Diagram showing the progression of cell cycle phases and drug addition with different processing speeds:

- **2N / G1**
- **S-phase**
- **4N / G2**
- **M-phase**
- **8N**

**Drug Addition**

- **1 CPU - Dual Core**
- **HPC - serial**
- **HPC - 32 CPUs**

End of experiment markers are indicated for each phase progression.
PK Modelling Approach

- Chosen to use a mechanistic (PBPK) model provided by PK-Sim™:
  - The model is preconstructed to include compartments for different tissues (useful for simulations of toxicity)
  - Extrapolation from mouse to human is based on physiological mechanisms so may be more accurate.
Pharmacokinetic Modelling - First Sketch

- We are currently using literature-derived and experimentally determined values for physicochemical properties of roscovitine.

- No calibration has been performed for distribution (active transport) and organ-specific metabolism (actually experimentally determined).

- Therefore, only the plasma concentration-time courses are used as an input to the pharmacodynamic model.
Pharmacokinetic Modelling

PK-Sim vs Nutley et al. (2005)

100mg/kg IV dose published by: Nutley et al.; Mol Cancer Ther 2–5;4(1), 125-139
Combined PK-PD Modelling

PK profile

Cell population

Conversion and rescaling

SystemCell® for HPC

Example single cell

128 unsync cells

- DNA content (virtualFACS)
- pHH3 (IVTI)
- Mitotic index

Dose scheduling

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...
• When administered at early G1 double Seliciclib dosing barely effects cell cycle length.

• When administered at late G1-G2, Seliciclib leads to sustained G2 arrest

Fernandez, E. et al, Abstract No 801, AACR Annual Meeting 2008, San Diego, CA
Multi-cell Combined PK-PD Modelling

Dose given at ZT3

Synchronised cell population

Dose given at ZT19

Unsynchronised cell population
Experimental Data

![Graph showing tumor weight over time for different treatments. The graph compares tumor weight as a function of time for CONTROL, ZT3, ZT11, and ZT19 treatments.]

Figure 2. Dosing time-dependent effects of Seliclib on tumor growth. Tumor weight change as a function of Seliclib administration time. ●, controls; ○, treated at ZT3; ▲, treated at ZT11; △, treated at ZT19. Treatment started on day 9 after tumor inoculation. Arrows, days of drug injection. Thirty-six controls and 32 mice were allocated to each treatment group. Points, mean; bars, SE. Differences between controls and animals treated at ZT3, ZT11, or ZT19 were validated with ANOVA (P < 0.001).

Seliclib toxicity was the lowest following dosing at ZT3 (lethal toxicity rate, 3.1%) compared with ZT11 (6.2%) or ZT19 (21.9%; P = 0.07, Fisher’s exact test).

Perspectives - Future work

- Simulate effects of Seliciclib on apoptosis
- Add regulation of apoptosis by circadian clock (balance cell division/cell death)
- Models for each organ - calibrated with experimental data
- Adapting model for Human (clinical trial design)
- New dosing regimen and delivery protocols for cancer drugs
Thank You

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